Optimal scan time for fluorine-18 fluorodeoxyglucose positron emission tomography in breast cancer

A.R. Boerner[1], M. Weckesser[1], H. Herzog[2], T. Schmitz[2], W. Audretsch[3], U. Nitz[4], H.G. Bender[4], H.-W. Mueller-Gaertner[1]

[1] Department of Nuclear Medicine, University Hospital Düsseldorf, Germany
[2] Institute of Medicine, Research Centre Jülich, Germany
[3] Department of Senology, City Hospital Düsseldorf, Germany
[4] Department of Gynaecology and Obstetrics, University Hospital Düsseldorf, Germany

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Abstract. Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) has proven useful in the differentiation of various tumour entities, including breast cancer. In patients with primary breast cancer we performed a 3-h imaging protocol to examine possible improvements in tumour detectability and image contrast. Twenty-nine patients with primary breast cancer with a diameter of ≥2 cm that was demonstrated to be malignant by biopsy or surgery were injected with 370–740 MBq ^{18}F-FDG and scanned in the prone position. Data were acquired 0–40 min, 1.5 h and 3.0 h after injection. After correction for measured attenuation, decay and scatter and iterative reconstruction, standardised uptake values (SUVs) and tumour-to-non-tumour and tumour-to-organ ratios were calculated. Visual analysis was performed using transverse, sagittal and coronal slices as well as 3D reprojection images. Tumour-to-non-tumour and tumour-to-organ ratios were significantly higher for the 3-h images than for the 1.5-h images. SUVs did not increase to the same extent. Lesion detectability was 83% in 1.5-h images compared to 93% in 3-h images. We conclude that tumour contrast in breast cancer is improved by starting the PET acquisition at 3 h p.i. rather than at 1.5 h p.i.

Key words: Breast cancer – Fluorine-18 fluorodeoxyglucose – Positron emission tomography – Tumour-to-non-tumour ratio – Contrast parameters

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Introduction

Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) has proven useful in the primary detection and follow-up of many tumours including breast cancer [1–6], in which there is an over-expression of Glut1 glucose transporters [7]. Nevertheless, the significance of FDG PET for clinical management and outcome in breast cancer is still uncertain [8]. On the other hand, FDG PET seems beneficial in the diagnosis of recurrent, metastatic [9, 10] or multifocal disease, in therapy monitoring [11, 12] and even in directing surgery [13]. For the re-staging of breast cancer patients, FDG PET appears to be the most accurate method available [14].

One reason for these dicrepancies and for the non-optimal specificity of FDG PET [15] may be the use of different technical and methodological approaches. With regard to variation in normal tissue FDG uptake [16], the use of standardised uptake values (SUVs) [3, 17, 18] should be useful in the assessment of PET data and the evaluation of glucose hypermetabolism; however, a critical issue in this respect is the time interval between FDG injection and measurement. SUVs obtained from data acquired 30–60 min after FDG administration have been applied in the differentiation of breast malignancies [19–21], but since inflammatory lesions accumulate FDG more early and more intensely than malignancies [22], the detectability of malignant foci may be impaired. Therefore, we prospectively and pre-operatively evaluated a 3-h acquisition protocol in 29 patients with breast cancer. FDG PET findings recorded at 1.5 and 3 h post injection (p.i) were compared with regard to SUVs, target-to-non-target and target-to-background ratios and qualitative blind reading by physicians.

Correspondence to: A.R. Boerner, Research Centre Jülich, Institute of Medicine, D-52425 Jülich, Germany

Materials and methods

Patients. Twenty-nine female patients were investigated, three of them repeatedly, because of focal breast lesions highly suggestive of breast cancer magnetice resonance imaging (MRI) and mammography. The patients' ages ranged from 34 to 63 years. All tumours were histologically proven using jet biopsies or surgery. Patient and tumour characteristics are shown in Table 1. Diabetic patients were excluded. All patients were fasted for at least 12 h and had blood glucose levels below 100 mg%. To be eligible for

Table 1. Patient and tumour characteristics

	Patient age (years) (median±SEM*)	No.	Tumour diameter (cm) (median±SEM*)	Oestrogen receptor positive (No.)	Tumour staging (lowest – highest stage)
Ductal invasive	45±8	18	2.9±0.6	5/18	pT2N0M0G2 – pT4N1M0G3
Lobular invasive	47±2	7	3.5±1.0	3/7	pT2N0M0G2 – pT4N1bM1G2
Inflammatory	40±2	2	6.3±2.2	0/2	pT2N1aM0G3 – pT4N2M1G3
Other	46±4	2	4.2±0.2	0/2	pT3N1M0 – pT4aN1M1

the protocol, patients had to be able and willing to lie on a PET bed in the prone position for a total of more than 3 h. Informed consent was obtained beforehand.

Methods. In all patients, transmission scans (≥900 s or ≥10^6 counts per bed position) in the prone position were performed prior to injection of 370–740 MBq of ^{18}F-FDG. A CTI ECAT EXACT HR + [full-width at half-maximum (FWHM) 4.5 mm, 15 cm transaxial field of view (FOV)] and a GE/SCX PC 4096 WB+ (FWHM 5.1 mm, 10 cm transaxial FOV) PET scanner were employed. Immediately after injection the first scan was started with the subsequent scans starting at 1.5 and 3 h.

After correction for random and scattered coincidences, dead time and decay, data were reconstructed with an iterative algorithm. Documentation carried out as 3D maximum re-projection in six whole-body views (anterior, posterior, right and left lateral,

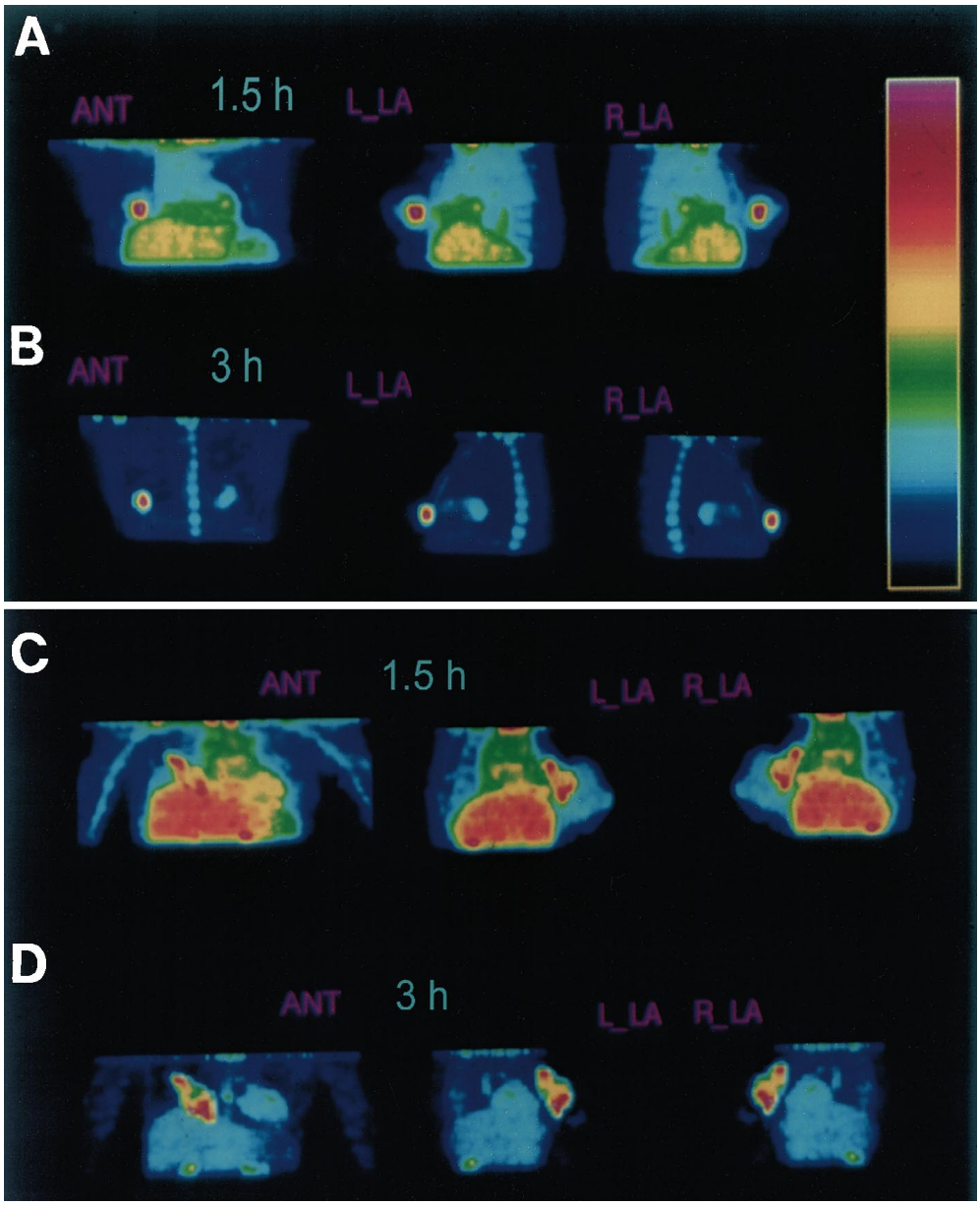

Fig. 1A–D. Two examples of the visualisation of large breast cancers (3.5 and 7.6 cm in maximum diameter) 1.5 and 3 h p.i. **A** Lobular invasive breast cancer; images obtained 90 min after injection of 550 MBq ^{18}F-FDG. **B** Same patient as in A, images obtained 180 min after injection. **C** Ductal invasive breast cancer; images obtained 90 min after injection of 560 MBq ^{18}F-FDG. **D** Same patient as in C; images obtained 180 min after injection

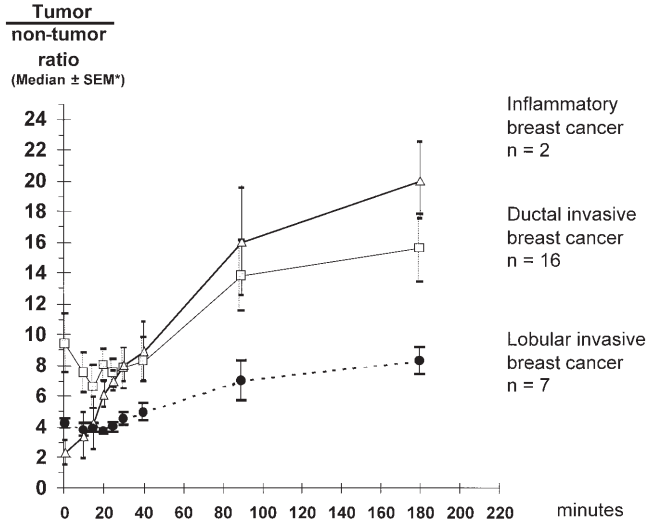

Fig. 2. Changes in tumour-to-non-tumour ratios (median ±SEM*) over time in the three predominant tumour types: lobular invasive, ductal invasive and inflammatory breast cancer

Table 2. SUVs at 1.5 and 3 h p.i. (*n* = 27 tumours)

1.5 h p.i. (median±SEM*)	3 h p.i. (median±SEM*)	Increase (%)
6.6±5.0	11.8±6.6	79

right and left anterior oblique) and in coronal, sagittal and transverse slices. The quantitative evaluation was based on a region of interest (ROI) analysis and yielded SUVs for the tumour as well as tumour-to-non-tumour (= contralateral breast), tumour-to-background (= mediastinum) and tumour-to-organ (= myocardium, liver and bone marrow) ratios. SUVs were calculated as decay-corrected ROI maximum/tumour (kBq/g) divided by injected activity/body weight (MBq/kg).

The number of pathological lesions was determined independently by three experienced physicians without knowledge of the patients' histories.

Statistics. Kolmogorov-Smirnov tests failed to show a normal distribution for any of the parameters tested. Statistical analysis was carried out by computing the median and standard error of the median [SEM* = (max.–min. value): 3.4641] unless stated otherwise, and by performing non-parametric tests (Wilcoxon test, Mann-Whitney *U* test, or Kruskal-Wallis test).

Results

Patients with ductal invasive, lobular invasive and other breast cancers showed no significant differences with regard to age, tumour stage or percentage of oestrogen receptor-positive tumours. The two patients with inflammatory cancers were slightly younger and had larger tumours at presentation. Typical examples of the visualisation of tumours 1.5 and 3 h p.i. are shown in Fig. 1. Fig. 2 illustrates the tumour-to-non-tumour ratios over time for the three predominant tumour types. Tumours were more clearly delineated on the later scans. Of 29 histologically proven primary breast cancers, 24 were diagnosed on the scans done at 1.5 h p.i. Examining the scans acquired 3 h after injection, 27 of the 29 tumours were adjudged pathological. Two breast tumours, both invasive ductal cancers, were visualised neither on the early nor on the late scans. In 4 of 29 patients a complete and accurate diagnosis was possible only by reference to the late images. Thirteen multifocal tumours appeared diffuse on the early scans but were clearly depicted on the 3-h scans. Lymph node involvement was present in 18 patients and was correctly diagnosed on all 3-h scans, whereas it was not visible in six patients on the 1.5-h scans. Visual analysis indicated no advantages of early over late imaging as no primary tumour or metastasis was diagnosed only by reference to early scans.

Due to a large variance, SUVs (Table 2) did not differ significantly at the two scan times, being 6.6±5.0 at 1.5 h versus 11.8±6.6 at 3 h after injection (representing an enhancement of approximately 80%). In contrast, tumour-to-background and tumour-to-non-tumour ratios as well as tumour-to-liver, tumour-to-bone marrow, tumour-to-mediastinum and tumour-to-myocardium ratios rose significantly (Table 3).

Discussion

Previous studies were able to demonstrate that about 10% of breast cancers do not accumulate FDG [23]. Our findings were similar, in that 2/29 patients were not correctly diagnosed by reference to the 3- and 1.5-hour scans. Comparing the scan times employed in our study, the results provide evidence that tumour contrast and de-

Table 3. Results in respect of contrast parameters at 1.5 and 3 h p.i. (*n* = 27 tumours)

	1.5 h p.i. (median±SEM*)	3 h p.i (median±SEM*)	Increase at 3.0 h versus 1.5 h (%)	Significance (Wilcoxon test)
Tumour/breast (tumour/non-tumour)	3.4±1.3	14.7±6.8	332	0.003
Tumour/mediastinum (Tumour/background)	1.2±0.6	6.1±3.0	408	0.001
Tumour/myocardium	0.8±0.5	3.2±1.2	300	0.003
Tumour/bone marrow	1.1±0.9	4.0±2.2	263	0.01
Tumour/liver	1.0±0.7	3.4±2.0	240	0.008

tectability are better at 3 h p.i. If glucose hypermetabolism is present, the low levels of glucose-6-phosphatase expressed by breast tissue and tumours derived therefrom prevent early washout of the radioactive label. Comparisons of glucose metabolism in breast and lung cancer revealed significantly higher glucose transport and utilisation but also an early washout of radioactive label in lung cancer [20, 24], resulting in superiority of 1-h FDG scans.

The goal in FDG-PET in patients with breast cancer must be to enhance diagnostic accuracy. This is to be achieved by avoiding non-diagnostic scans with considerable FDG accumulation in normal glandular breast tissue, equivocal target-to-background ratios and poor image quality (all of which obscure small tumour foci). The data presented demonstrate that sensitivity is increased by scanning at 3 h rather than 1.5 h p.i.

No purely inflammatory or other benign lesions were observed in our study as MRI proved highly accurate. Still, judging from other tumours like pancreatic [25] or head/neck masses [26] the problem of differentiating inflammatory disease from malignancy will not be solved by changes in imaging procedures. Inflammatory cells accumulate FDG early and intensively, with SUVs in the same range as many malignant tumours. Washout phenomena are not reported earlier or more often in inflammation [22]. However, as tumour-to-bone marrow ratios are significantly higher at 3 h than at 1.5 h p.i. (Table 2) (probably as a consequence of measurable efflux of radioactivity from white blood cells and their precursors), there is hope that better differentiation of tumour and inflammation will be possible using late scans.

The metabolite basis for interpreting FDG imaging data is far less developed [27] compared to visual analysis. Scan protocols have varied with regard to the timing of data acquisition, depending on the tumour under investigation. According to Fischman and Alpert [28], most of the radiation emitted from tissue within the first hour after injection comes from intracellular FDG-6-PO4, and in the absence of significant glucose-6-phosphatase activity the concentration of FDG in tissue will eventually reach a plateau representing the metabolically trapped ^{18}F label. As yet, there is no evidence that breast malignancies achieve FDG plateau concentrations within 60 min after injection [29]. The results presented to date clearly show that the FDG kinetics of every tumour type studied clinically must be better understood in order for more meaningful results to be obtained [28]. Recently, findings of a correlation between prognostic indices like histopathological grading or p53 expression and FDG uptake have been reported [30]. As tumour-to-breast tissue ratios tend to change rapidly over the first hour post injection, a suitable later scan time seems more for longitudinal studies using FDG PET. Use of later scanning should reduce biological and inter-observer variability and improve evaluation of tumour glycolytic rates [31]. Furthermore, patients may be spared time-consuming procedures in the prone position, which is essential for differentiation of breast tissue and the underlying chest wall as well as for any overlay technique with MRI data.

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